Aelami et al. *Antimicrobial Resistance and Infection Control* 2014, **3**:30
http://www.aricjournal.com/content/3/1/30

ANTIMICROBIAL RESISTANCE & INFECTION CONTROL

REVIEW Open Access

Ventilator-associated pneumonia in neonates, infants and children

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Abstract

Ventilator-associated pneumonia (VAP) is relatively common in mechanically-ventilated children, but there is a wide variation in reported VAP rates, depending on settings and geographical regions. Surveillance definitions in children are challenging. Although these are provided by the German nosocomial infection surveillance system and an independent Dutch group, the combination of clinical and radiologic signs leaves room for interpretation. Of note, the United States Centers for Disease Prevention and Control guidelines do not offer algorithms for neonates. Despite the fact that most experts agree on the low sensitivity and specificity of existing definitions, little has changed over the past years. However, the number of studies reporting on VAP prevention programs has increased in recent years. Single interventions, such as chlorhexidine mouth wash or stress ulcer prophylaxis, were not effective. Successful prevention programs combined multiple interventions, such as hand hygiene, glove and gown use for endotracheal tube manipulation, backrest elevation, oral care with chlorhexidine, stress ulcer prophylaxis, cuff pressure maintenance where appropriate, use of orogastric tubes, avoidance of gastric overdistension, and elimination of non-essential tracheal suction. These multimodal strategies have proved to be successful among neonates, infants, and children. Importantly, they are applicable in high- as well as in low- and middle-income countries. This review provides an update of VAP incidence rates and summarizes current knowledge on its epidemiology, risk factors, surveillance definitions, and prevention programs in the pediatric setting.

Keywords: Ventilator-associated pneumonia, Children, Neonates, Healthcare-associated infection

Introduction

Healthcare-associated infections (HAIs) are associated with morbidity, mortality, and prolonged hospitalization, and represent a serious threat to patient safety. Hospitalized children are a particularly vulnerable population [1]. The incidence of HAI in adult and pediatric intensive care units (PICUs) is high. This is due to the many invasive procedures and frequent antibiotic use, which put the patients at risk for infection and promote the emergence of multidrug-resistant organisms [2]. The use of invasive devices in PICUs, such as central vascular lines and mechanical ventilation, is similar to adult intensive care and thus the burden of ventilator-associated pneumonia (VAP) and other HAIs is also similar [3]. In this review, we describe the epidemiology of VAP, summarize risk factors, and discuss effective prevention measures in PICUs and neonatal ICUs (NICUs).

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Review

Literature search and selection strategy

A Medline search was performed for publications prior to 1 May 2014 using the following search (MeSH) terms: “pneumonia, ventilator associated” AND (child* OR neonat* OR infant* OR pediatr* OR paediatr*) and also pneumonia AND (nosocomial OR “healthcare-associated” OR “healthcare associated” OR “health care associated”) AND (ventilat* OR intubat* OR respirat*) AND (child* OR neonat* OR infant* OR pediatr* OR paediatr*). Cross-referencing from retrieved publications was used to complete the search, including manual searches of cited references and relevant abstracts. Publications were eligible to be analyzed if they addressed VAP in any inpatient pediatric population. A total of 443 titles and abstracts were screened; 95 were retained for discussion in this review.

Table 1 Case definitions of hospital-acquired pneumonia in children stratified by different age groups

Neonates	Onset >72 h after birth and one of the following radiologic criteria:
	–new or progressive infiltrates
	–consolidations
	–adhesions or fluid in lobar fissures/pleura
	And
	Worsening gas exchange (SaO_2 ↓; O_2 requirement ↑; Ventilation parameters ↑)
	And
	Four of the following signs and symptoms:
	–fever (>38.0°C), hypothermia (<36.5°C), or temperature instability
	–new onset or increasing bradycardia (<80/min) or tachycardia (>200/min)
	–new onset or increasing tachypnoea (>60/min) or apnoea (>20 seconds)
	–new onset or increasing signs of dyspnoea (retractions, nasal flaring, grunting)
	–increasing production of respiratory secretions and need for suctioning
	–purulent tracheal secretion
	–isolation of a pathogen in respiratory secretions
	–elevated C-reactive protein (>20 mg/L)
	I/T-ratio >0.2
Infants: 2–11 months	One of the following radiologic criteria:
	–new or progressive infiltrate
	–consolidations
	–cavitations
	–pneumatoceles
	And
	Worsening gas exchange (SaO_2 ↓; O_2 requirement ↑; Ventilation parameters ↑)
	And
	Three of the following signs and symptoms:
	–fever (>38.0°C), hypothermia (<36.5°C), or temperature instability
	–leucopenia (<4000 WBC/mm^3) or leucocytosis (≥15,000 WBC/mm^3) with left shift (≥10% band forms)
	–new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
	–apnoea or dyspnoea (tachypnoea, nasal flaring, retraction of chest wall, grunting)
	–wheezing, rales, or rhonchi
	–cough
	–bradycardia (<100/min) or tachycardia (>170/min)
Children: 1–16 years	One of the following radiologic criteria:
	–new or progressive and persistent infiltrate
	–consolidation
	–cavitation
	And
	Three of the following signs and symptoms:
	–fever (>38.4°C) or hypothermia (<36.5°C)
	–leukopenia (<4000 WBC/mm^3) or leucocytosis (≥15,000 WBC/mm^3)
	–new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements
	–new onset or worsening cough or dyspnoea, apnoea, or tachyponea
	–rales or bronchial breath sounds
	–worsening gas exchange (SaO_2 ↓; O_2 requirement ↑; Ventilation parameters ↑)

SaO_2: Oxygen saturation; I/T-ratio: immature to total neutrophil ratio; WBC: white blood cell count; ↑: increase; ↓: decrease.

Definitions

A uniform definition of VAP needs to have the capacity to be relevant for clinical trials, while balancing the risks of experimental therapy and sampling procedures with potential benefits for study patients [4]. If the definition of VAP is already controversial for adults, it is even more challenging for children, in particular for ventilated neonates. The starting point of the recent United States (US) Centers for Disease Prevention and Control (CDC) definitions for adults is a ventilator-associated complication (VAC), which is further narrowed towards infectious VAC and then towards possible or probable VAP, according to additional diagnostics [5]. However, It is not clear whether this algorithm can be applied to children in different age groups and, thus, the conventional CDC definitions of hospital-acquired pneumonia for children and neonates remain valid for the time being [6]. These definitions do not specify between "ventilated" or "non-ventilated" and the use of the term "VAP" depends on the time on ventilation (48 h or longer). The German national nosocomial infection surveillance system (Krankenhaus Infektions Surveillance System [KISS]) offers a definition for very low birth weight infants in their "Neo-KISS" module [7]. A Dutch study group established their own definition for VAP in neonates, which are more inclusive than the CDC definitions [8]. Table 1 summarizes the definitions of hospital-acquired pneumonia by stratifying age groups into neonates, infants (≤1 year), and children (>1 year to ≤ 16 years). All definitions combine clinical and radiologic signs. In addition, the CDC and the European Centre for Disease Prevention and Control

(ECDC) definitions further distinguish between definite, probable, and possible healthcare-associated pneumonia, based on microbiologic findings (Table 2) [9]. Clinical and radiologic findings lack sensitivity and specificity. However, tracheal aspirate cultures have also low sensitivity (31-69%) and specificity (55-100%). A positive tracheal culture alone does not discriminate between bacterial colonization and respiratory infection. Bronchoalveolar lavage (BAL) provides better results, but the range of sensitivity (11-90%) and specificity (43-100%) is large.

Clinical criteria

Clinical criteria for healthcare-associated pneumonia include fever, leukocytosis or leucopoenia, purulent secretions, new or worsening cough, dyspnoea, tachypnoea, crackles or bronchial breath sounds, and worsening gas exchange. These criteria are nonspecific and their sensitivity and specificity relative to the underlying pathology is poor [2]. Clinical findings must be combined with radiologic and microbiologic findings. In a study of 70 children with VAP, the modified clinical pulmonary infection score (mCPIS) of six or higher had a sensitivity of 94%, a specificity of 50%, a positive predictive value of 64%, a negative predictive value of 90%, and positive and likelihood ratios of 1.9 and 0.1, respectively [10].

Radiologic criteria

Radiologic criteria include the presence of new or progressive pulmonary infiltrates, adhesions or fluid in lobar fissures/pleura, cavitations, air bronchograms, or pneumatoceles on chest x-rays. The presence of air bronchograms has a higher sensitivity (58–83%) than "evolving infiltrates" (50–78%) [2]. Sequential chest x-rays (days −3, 0, 2, 7) help to confirm healthcare-associated pneumonia in complex cases, such as children with underlying cardiac or pulmonary disease. Onset and progression of pneumonia in imaging is fast, but improvement takes time.

Microbiologic criteria

Respiratory cultures are obtained by tracheal aspirates, bronchoalveolar lavage (BAL), non-bronchoscopic BAL, or protected brush specimens (PBS) [10]. Thresholds are summarized in Table 2.

Epidemiology

Healthcare-associated pneumonia was the most common HAI in five studies [11-15], and second only to bacteremia in another two reports [16,17]. The range of VAP incidence density rates in both children and neonates is large. Rates as low as 1/1000 ventilator-days and as high as 63/1000 ventilator-days have been reported (Table 3). The incidence follows a geographical distribution and depends on the type of hospital and the country income level. A surveillance study from the International Nosocomial Infection Control Consortium (INICC) identified higher VAP rates in academic compared to non-academic hospitals [18]. The same study reported higher rates in lower-middle-income compared to upper-middle-income countries. Extreme PICU rates have been reported from India (36.2%) [19] and Egypt (31.8/1000 ventilator-days) [20]. Surveys in the USA and Germany found consistently lower rates (Table 3) [21-23]. However, high rates were reported also by high-income countries. A European multicenter study found that 23.6% of children admitted to a PICU developed VAP [24]. An Italian study identified 6.6% children with VAP among 451 on mechanical ventilation [25], and a mixed PICU in Australia identified 6.7% children with VAP among 269 on mechanical ventilation [26].

VAP is also common in the NICU and proportions between 6.8% and 57.0% of HAIs have been reported [34,60-66]. A Spanish study identified VAP in 9.1% of 198 neonates on mechanical ventilation [67]. In a Taiwanese NICU, 11.4% of 528 neonates had one or more HAIs, with VAP contributing to 18.6% [68]. An INICC

Table 2 Classification of hospital-acquired pneumonia in children based on microbiological results

Definite VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) and has one of the following:
	−same pathogen isolated from bronchial secretions/BAL and blood
	−pathogen or virus isolated from lung biopsy, or positive growth in culture of pleural fluid, or histopathologic examination with evidence of pneumonia manifested as abscess formation, positive culture of lung parenchyma, or fungal hyphae
	−Pathogen or virus isolated from BAL (bacteria $\geq 10^4$ CFU/ml), or ≥5% of BAL-obtained cells contain intracellular bacteria on direct microscopic exam, or protected brush with a threshold of $\geq 10^4$ CFU/ml, or distal protected aspirate with a threshold of $\geq 10^4$ CFU/ml, or positive exams for particular microorganisms (*Legionella*, *Aspergillus*, mycobacteria, *Mycoplasma*, *Pneumocystis jirovecii*)
Probable VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) and has one of the following:
	−pathogen isolated from BAL (bacteria $<10^4$ CFU/ml)
	−pathogen or virus isolated from bronchial secretions, or quantitative culture of lower respiratory tract specimen (endotracheal aspirate) with a threshold of bacteria $\geq 10^6$ CFU/ml
Possible VAP	A child who fulfils the case definitions for hospital-acquired pneumonia (Table 1) with non-quantitative lower respiratory tract specimen culture or no positive microbiology, but has been treated for hospital-acquired pneumonia

BAL: bronchoalveolar lavage; CFU: colony-forming units.

Table 3 Incidence densities and proportions of ventilator-associated pneumonia in pediatric settings

Region	Reference (Author, Country, Year of publication, Ref No)	Setting	Patients	VAP*	VD*	Incidence density (N/1000 ventilation-days)	%**
Middle	Afjeh, Iran, 2012 [27]	NICU*	[2]81	14	1207	11.6	17.3
East/Persia	Almuneef, Saudi Arabia, 2004 [28]	PICU*	[2]361	37	4173	8.9	10.3
	Shaath, Saudi Arabia, 2013 [29]	Cardiac surgery	[1]137	9	306	29.4	6.6
South Asia	Awasthi, India, 2013 [19]	PICU*	[2]105	38	-	-	36.2
East Asia	Yuan, China, 2007 [30]	NICU*	[2]259	52	1130	46.0	20.1
	Navoa-Ng, Philippines, 2011 [31]	PICU*	[3]252	6	391	0.44	2.4
	Navoa-Ng, Philippines, 2011 [31]	NICU*	[3]1813	1	2279	12.8	0.06
	Xu, China, 2007 [32]	NICU*	[3]3942	143	2259	63.3	3.6
	Cai, China, 2010 [33]	NICU*	[3]1159	38	779	48.8	3.3
Europe	Geffers, Germany, 2008 [21]	NICU* (<1500 g)	[3]8677	176	64090	2.7	2.0
	Leistner, Germany, 2013 [22]	NICU* (<1500 g)	-	345	158024	2.2	-
	Tekin, Turkey, 2013 [34]	NICU*	[3]6932	76	11939	6.4	1.1
	Yalaz, Turkey, 2012 [35]	NICU*	[2]162	40	2907	13.8	24.7
	Patria, Italy, 2013 [25]	PICU*	[3]451	30	-	-	6.7
	Hentschel, Switzerland, 2005 [36]	NICU*	[1]21	1	80	12.5	4.8
	Roeleveld, Netherlands, 2011 [37]	Cardiac surgery	[1]125	11	644	17.1	8.8
	Gastmeier, Germany, 2002 [38]	Burn unit	[3]41	8	145	55.2	19.5
	Oezdemir, Turkey, 2011 [39]	PICU*	[3]203	-	-	15.7	-
	Jordan Garcia, Spain, 2014 [40]	PICU*	[3]300	4	422	9.5	1.3
	Turkish Neonatal Society; 2010 [41]	NICU*	[3]9359	-	-	-	1.7
North	Edwards, USA, 2008 [23]	PICU*	-	176	85809	2.1	-
America	Edwards, USA, 2008 [23]	NICU*	-	410	203466	2.0	-
	Edwards, USA, 2007 [42]	PICU*	-	81	32936	2.5	-
	Edwards, USA, 2007 [42]	NICU*	-	121	63075	1.9	-
	Hocevar, USA, 2012 [43]	NICU*	-	701	336527	2.1	-
	Stover, USA, 2001 [44]	PICU*	-	-	-	3.7	-
	Stover, USA, 2001 [44]	NICU*	-	-	-	2.5	-
	Apisarnthanarak, USA, 2003 [45]	NICU* (ELBW)	[2]211	24	4173	5.8	11.4
	Elward, USA, 2002 [46]	PICU*	[1]595	34	2931	11.6	5.1
	Weber, USA, 1997 [47]	Burn unit	[1]40	7	614	11.4	17.5
	Martinez-Aguilar, Mexico, 2001 [48]	PICU*	-	44	1571	28	-
South	Abramczyk, Brazil, 2003 [11]	PICU*	[3]515	40	2120	18.7	7.8
America	Pessoa-Silva, Brazil, 2004 [49]	NICU*	[3]4878	83	10494	7.9	1.7
	Araujo da Silva Brazil, 2012 [50]	Homecare	[1]9	23	3394	6.8	-
	Casado, Brazil, 2011 [51]	PICU*	[1]366	39	1439	27.1	10.7
	Duenas, Argentina, 2011 [52]	PICU*	[3]1145	93	7709	12.1	8.1
	Duenas, Argentina, 2011 [52]	NICU*	[3]1270	139	8634	16.1	10.9
	Becerra, Peru, 2010 [53]	PICU*	[3]414	27	3420	7.9	6.5
	Fernandez Jonusas, Argentina, 2011 [54]	NICU*	[3]1530	6	3157	1.9	0.4
Africa	Rasslan , Egypt, 2012 [20]	PICU*	[3]143	18	567	31.8	12.6
	Rogers, South Africa, 2014 [55]	Burn unit	[2]92	41	-	30.0	40.2
	El-Kholy, Egypt, 2012 [56]	PICU*	[1]211	54	1478	36.5	25.6
	El-Kholy, Egypt, 2012 [56]	NICU*	[1]127	26	1003	25.9	20.5

Table 3 Incidence densities and proportions of ventilator-associated pneumonia in pediatric settings *(Continued)*

	Ben Jaballah, Tunisia, 2006 [57]	PICU/NICU*	[3]340	7	1591	4.4	2.1
	Badr, Egypt, 2011 [58]	NICU*	[2]56	32	315	101.6	57.1
	El-Nawawy, Egypt, 2006 [59]	PICU*	-	-	-	10.9	-
Australia	Gautam, Australia, 2012 [26]	PICU*	[2]269	18	2564	7.0	6.7

*NICU: neonatal intensive care unit; PICU: pediatric intensive care unit; VAP: ventilator-associated pneumonia; VD: ventilation days.
**Proportion of patients with ventilator-associated pneumonia compared to patients included in the study (admissions or patients on ventilation).
[1]Patients on mechanical ventilation for 24 h or more.
[2]Patients on mechanical ventilation for more than 48 h.
[3]All admitted patients.

survey summarizing results from 30 NICUs in 15 countries reported significantly higher VAP rates in academic compared to non-academic institutions [69]. VAP incidence densities in an Iranian and Turkish NICU were 13.8/1000 and 11.6/1000 ventilator-days, respectively [27,35]. A higher incidence was reported in another Iranian study with 42% of 38 neonates on mechanical ventilation [70]. Table 4 summarizes birth weight-dependent numbers from different studies [8,21-23,42-44,49,71].

Several studies from the USA, Italy, and Iran found that VAP prolonged mechanical ventilation by approximately 8–12 days [25,70,72,73], and this may even be as high as 56 days in extremely preterm neonates [46]. Prolonged length of stay was the main driver of attributable costs of up to US$ 1040 in Iran and US$ 51,157 in the USA [70,73]. There are no data on the attributable mortality of VAP. The mortality of HAI in the PICU is estimated to range between 5-14% [27,44], to which VAP may significantly contribute (P = 0.04) [25].

Risk factors

Ventilation was the most important identified risk for HAI in a prevalence study of 21 hospitals in Mexico (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.2-4.1) [74]. Reintubation (OR, 2.7; CI, 1.2-6.2) and transport out of the PICU (OR, 8.9; CI, 3.8-20.7) were significant risk factors identified in a US PICU [74]. Other extrinsic risk factors include prior antibiotic therapy (OR, 2.89; CI, 1.41-5.94), bronchoscopy (OR, 4.48; CI, 2.31-8.71), immunosuppressive drugs (OR, 1.87; CI, 1.07-3.27), and the use of enteral feeding (OR, 8.78; CI, 2.13-36.20) [75-77]. A number of intrinsic factors predisposing for VAP have been reported, such as young age (<12 months) [75,78], subglottic or tracheal stenosis (P = 0.02), trauma (P = 0.02), tracheostomy (P = 0.04) [72], gastroesophageal reflux [79], immunodeficiency [28], neuromuscular blockade [28,75,80], genetic syndromes (OR, 2.04; CI, 1.08-3.86) [46,76], and gender (female: OR, 10.32; CI, 2.9-37.2) [77].

In neonates, the main risk factors are low birth weight (hazard ratio [HR], 1.37; CI, 1.0-1.9]) and mechanical ventilation (HR, 9.7; CI, 4.6-20.4) [8]. Time of mechanical ventilation was a main factor in Spanish (OR, 1.1; CI,1.1-1.2) [67], Chinese (OR, 4.8; CI, 2.2-10.4) [30], and Iranian studies (P <0.001) [70]. Reintubation, absence of tube feeding, and absence of stress ulcer prophylaxis were risk factors in Australia [26]. In an Italian study, reintubation (P < 0.001), tracheostomy (P = 0.04), and enteral feeding (P = 0.02) were associated with VAP [25]. Risk factors for VAP are summarized in Table 5.

Microorganisms

The microorganism type and antibiotic susceptibility are variable according to the geographical region (Figure 1). Gram-negative pathogens predominate, but their contribution is exceptionally high in Asia. Overall, the most common pathogens are *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Enterobacteriaceae.* In Europe and North America *Staphylococcus aureus* predominate [8,77,81]. In Asia, most pathogens are multidrug-resistant [82-84]. A Greek group reported 65 children with 71 infections

Table 4 Incidence densities of ventilator-associated pneumonia in neonatal intensive care units stratified by birth weight

Weight categories	Edwards USA 2007 [42]	Edwards USA 2008 [23]	Rosenthal INICC 2010 [71]	Hocevar USA 2012 [43]	Stover USA 2001 [44]	Pessoa-Silva Brazil 2004 [49]	Van der Zwet The Netherlands 2005 [8]	Geffers Germany 2008 [21]	Leistner Germany 2013 [22]
≤ 750 g	2.5	2.6	11.8	2.4	3.5*	7.0*	19.7*	2.8*	2.3*
751-1000 g	2.2	2.1	9.2	2.1					
1001-1500 g	1.4	1.5	8.2	1.3	4.9	9.2	14.7	2.3	1.6
1501-2500 g	1.1	1.0	7.2	0.9	1.1	7.8	5.8	-	-
>2500 g	1.2	0.9	6.2	0.7	0.9	8.3	7.4	-	-

*Birth weight ≤1000 g.

Table 5 Risk factors for ventilator-associated pneumonia in pediatric and neonatal settings

Risk factor	Reference (Author, Ref No)	Setting	Patients	VAP, n	VAP, %	Odds ratio [95% CI]	P-value
Gender (female)	Srinivasan [77]	NICU/ PICU	60	19	32	10.3 [52.9-37.2]	<0.001
Genetic syndromes	Elward [46]	PICU	595	34	5.1	2.4 [1.0-5.5]	0.043
Trauma	Bigham [72]	PICU	2846	42	1.47	-	0.020
Post-surgical admission diagnosis	Srinivasan [77]	NICU/ PICU	60	19	32	10.0 [2.2-46.1]	0.003
Subglottic or tracheal stenosis	Bigham [72]	PICU	2846	42	1.47	-	0.020
PRISM III score >10	Roeleveld [37]	Cardiac surgery	125	11	8.8	4.4 [1.1-18.0]	0.041
Prolonged ventilation	Awasthi [19]	Ventilatory units	105	38	36.2	3.8 [1.4- 10.0]	0.008
	Casado [51]	PICU	366	39	10.7	1.0 [1.0-1.1]	0.017
Reintubation	Patria [25]	PICU	451	30	6.6	9.5 [3.3-26.8]	<0.001
	Elward [46]	PICU	595	34	5.1	2.7 [1.2-6.2]	0.011
Tracheostomy	Patria [25]	PICU	451	30	6.6	4.4 [1.0-20.0]	0.040
	Bigham [72]	PICU	2846	42	1.47	-	0.040
Bronchoscopy	Almuneef [28]	PICU	361	37	10.3	5.0 [1.7-15.3]	<0.001
Use of gastric tube	Casado [51]	PICU	366	39	10.7	2.9 [1.4-5.9]	0.003
Enteral feeding	Patria [25]	PICU	451	30	6.6	13.2 [1.5-114.2]	0.020
	Srinivasan [77]	NICU/PICU	60	19	32	8.8 [2.1- 36.2]	0.003
	Almuneef [28]	PICU	361	37	10.3	2.3 [1.1-4.8]	0.004
Prior antibiotic therapy	Almuneef [28]	PICU	361	37	10.3	2.5 [1.1-5.4]	0.026
Administration of blood products	Srinivasan [77]	NICU/PICU	60	19	32	0.1 [0.02- 0.6]	0.009
Use of sedatives/analgesics	Srinivasan [77]	NICU/PICU	60	19	32	77.5 [7.1- 844.6]	<0.001
	Casado [51]	PICU	366	39	10.7	2.5 [1.3-4.7]	0.007
Neuromuscular blockade	Da Silva [80]	PICU	317	-	5	-	0.010
Transport out of the PICU*	Elward [46]	PICU	595	34	5.1	8.9 [3.8-20.7]	<0.001

VAP: ventilator-associated pneumonia; PICU: pediatric intensive care unit.
*Transport out of the PICU for diagnostic procedures or medical interventions.

(20 VAP) due to carbapenem-resistant Gram-negative pathogens [85]. Isolates included *Pseudomonas* spp. (41.1%), *Acinetobacter* spp. (39.7%), and *Klebsiella* spp. (19.2%).

Prevention

Many interventions in different combinations have been shown to play a role in VAP prevention: hand hygiene, preferably with alcohol-based handrub; glove and gown use for endotracheal tube manipulation; backrest elevation of 30° to 45°; oral care with chlorhexidine; stress ulcer prophylaxis; cuff pressure maintenance; use of orogastric tubes; avoidance of gastric overdistension; and elimination of nonessential tracheal suction [86]. Oral care with chlorhexidine compared to placebo in 96 children on mechanical ventilation was not effective in reducing VAP in a Brazilian study [87]. Similar results were reported in a placebo-controlled study with high VAP rates in North India [88] and a randomized trial among children undergoing cardiac surgery in Brazil [89]. Gastroesophageal reflux is a constant incident in mechanically- ventilated children, with alkaline reflux more common than acidic reflux [79]. Thus, stress ulcer prophylaxis is rather unlikely to prevent VAP and, consequently, neither sucralfate nor ranitidine were effective in VAP prevention in a small study [90]. Two studies showed that VAP rates are lower in neonates undergoing nasal continuous positive airway pressure compared to the use of mechanical ventilation [21,36].

A prevention bundle reduced VAP from 7.8/1000 to 0.5/1000 ventilator-days ($P < 0.001$) in a US PICU with an estimated economy of 400 hospital-days and cost-savings of US$ 2,353,222 [73]. In another PICU, a bundle adapted to local needs by plan-do-study-act cycles reduced VAP rates in a similar manner [72]. The bundle addressed handling of ventilator circuits and oral suctioning, hand hygiene, regular oral care with chlorhexidine, and backrest elevation. By applying a multimodal intervention, three PICUs reduced the incidence of hospital-acquired pneumonia from 5.6 per 100 patients at baseline to 1.9 in the intervention ($P = 0.016$) [91]. An educational program targeting resident physicians and nurses in a PICU of a lower-middle-income country resulted in a non-significant VAP reduction of 28% ($P = 0.21$) [92]. A quality improvement intervention targeting

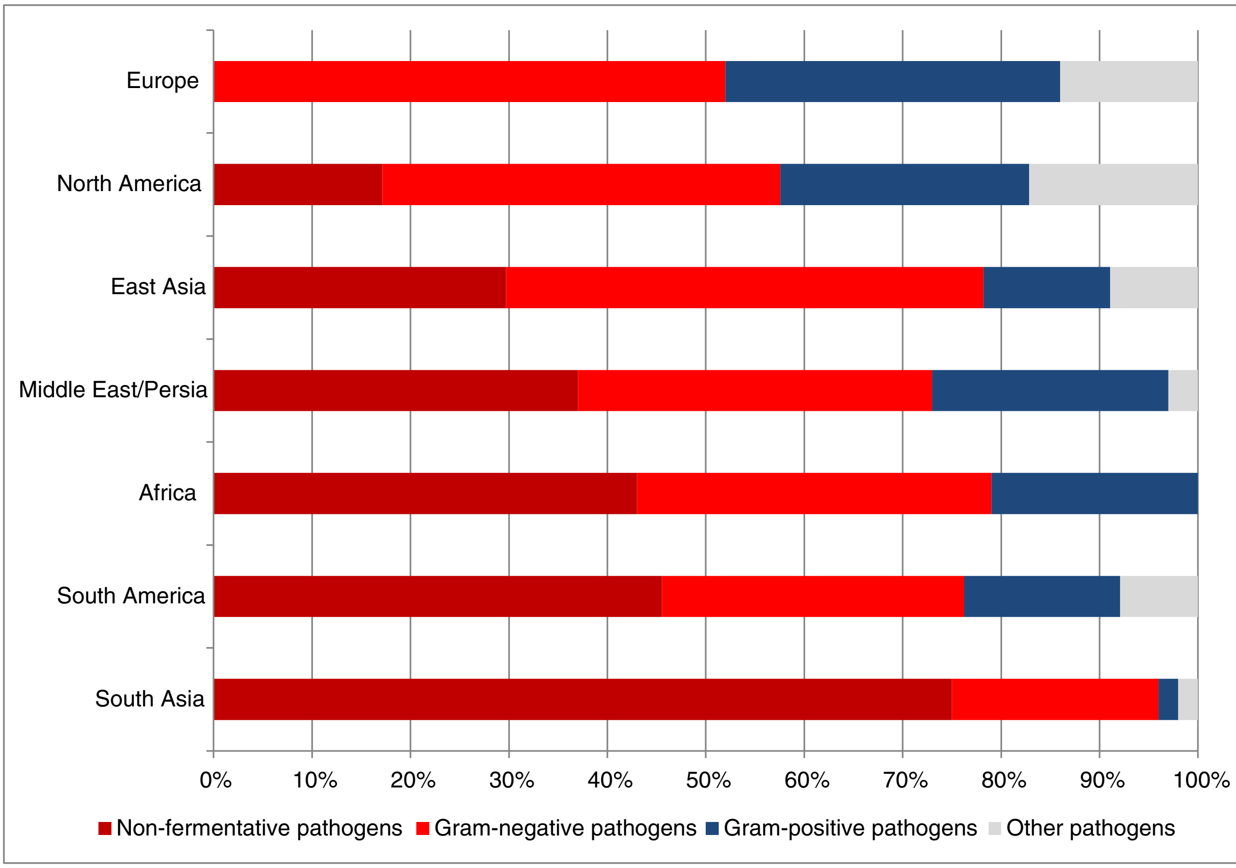

Figure 1 Geographical distribution of pathogens causing ventilator-associated pneumonia in children.

hand hygiene and establishing quality practices decreased VAP from 28.3/1000 to 10.6/1000 ventilator-days (P = 0.005), which was sustainable over a long-term, follow-up period [93]. In a before-after study in eight PICUs of five developing countries, the efficacy of a multidimensional infection control program including education, outcome surveillance, process surveillance, and feedback on VAP rates and performance reduced VAP from 11.7/1000 to 8.1/1000 ventilator-days (P = 0.02) [94]. The institution of a purpose-designed bundle by a nurse-led VAP surveillance program addressed backrest elevation; oral care using chlorhexidine; clean suctioning practice; ranitidine for all children not on full feeds; and four-hourly documentation [95]. After bundle implementation, no VAP was recorded over a 12-month period. The baseline ventilator-associated tracheobronchitis rate of 3.9/1000 ventilator-days was reduced to 1.8/1000 (P = 0.04) by implementing a multidisciplinary quality improvement initiative in another US PICU [96].

A strategy combining care practices with empowering the bedside nurse to lead bundle implementation in a NICU encouraged personal ownership and compliance with the bundle and finally reduced VAP by 31%, resulting in savings of 72 hospital-days and US$ 300,000 [97]. The INICC multidimensional infection control program was associated with significant reductions of VAP rates in the NICUs of 15 cities from 10 developing countries [98]. VAP rates at baseline and intervention were 17.8/1000 and 12.0/1000 ventilator-days, respectively [98]. Of 491 patients receiving mechanical ventilation in a Chinese NICU, the rate of VAP decreased from 48.8/1000 to 25.7/1000 ventilator-days and further diminished to 18.5/1000 after hospital relocation and establishing a bundle of comprehensive preventive measures (P < 0.001) [99].

Conclusion

VAP is common in mechanically-ventilated children with a wide variation of incidence density rates across geographical regions. Surveillance definitions are challenging in pediatric settings because the combination of clinical and radiologic signs leaves too much room for interpretation. This is particularly important in neonates, where CDC and INICC guidelines, and the German KISS program follows mainly the rationale of the definitions for older children. Gram-negative pathogens are the most common microorganisms, particularly *A. baumannii* and *P. aeruginosa*. However, there is a geographic variation with Gram-positive organisms more frequently observed in high-income compared to low- and middle-income countries. Similar to the evidence base of adult settings, a number of studies reported effective VAP prevention strategies. Successful programs combined multiple interventions, such as hand hygiene, glove and gown use for endotracheal tube manipulation, backrest elevation, oral care with chlorhexidine, stress ulcer prophylaxis, cuff pressure maintenance where appropriate, use of orogastric tubes, avoidance of gastric overdistension, and elimination of nonessential tracheal suction. When applied as a multimodal strategy by an interdisciplinary team, these interventions are most likely to be successful among neonates, infants, and children, and have proven effectiveness in high-, as well as in low- and middle-income countries.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MHA, ML and WZ carried out the literature review. MHA provided the first draft of the manuscript. WZ participated in the coordination of the review and finalized the manuscript. All authors read and approved the final manuscript.

Acknowledgments
We would like to thank Rosemary Sudan for editorial support.

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Received: 2 June 2014 Accepted: 21 September 2014
Published: 30 September 2014

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doi:10.1186/2047-2994-3-30
Cite this article as: Aelami et al.: Ventilator-associated pneumonia in neonates, infants and children. *Antimicrobial Resistance and Infection Control* 2014 **3**:30.